

Basophil activation in two cases of hydrochlorothiazide-induced noncardiogenic pulmonary edema

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Since the first case report by Steinberg in 1968, more than 50 cases of acute noncardiogenic pulmonary edema caused by hydrochlorothiazide (HCT) have been reported (1). Most cases have an acute onset of symptoms and rapid improvement with supportive treatment. The reaction developed either upon taking HCT for the first time or after having taken the drug previously without reaction. The majority of cases have a positive challenge test with HCT and tolerate furosemide (1). Some cases reveal transient leucopenia (2) and/or thrombopenia, likely because of pulmonary sequestration of neutrophils (3); however, blood eosinophils and total IgE tend to fall within normal values. When measured, specific IgE or IgG to HCT has been negative (4).

A 66-year-old man developed dyspnea and profuse sweating within 30 min of taking a single dose of 150 mg of irbesartan and 50 mg of HCT. Seven years ago, he had good tolerance to HCT. The second patient was a 49-year-old woman who experienced sudden onset of shortness of breath 40 min after taking a single dose of amiloride 5 mg and HCT 50 mg. Neither of them had previous

reaction to HCT. Both were admitted to the critical care unit with acute respiratory failure and hypotension. Chest X-rays showed interstitial infiltrates in both patients, and in patient 1 a CTscan showed bilateral pulmonary edema. Central venous pressure and all echocardiograms were normal. The two patients showed a favorable clinical course under supportive treatment (e.g., oxygen therapy, furosemide, methylprednisolone and dopamine). Blood analysis in both patients showed leukopenia with a normal white blood cell distribution (patient 1: 3500/mm³; patient 2: 500/mm³) with no other abnormalities in biochemistry or cardiac enzymes during acute phase. Both patients tolerated furosemide used as treatment for their acute episode. A bronchoalveolar lavage (BAL) was performed on patient 1 in the Intensive Care Unit, revealing the presence of a high number of neutrophils (64%) and activated eosinophils (10%), with a normal TCD4⁺/TCD8⁺ ratio (1.9), normal values for BAL in the healthy subjects: 80–95% macrophages, <15% lymphocytes, 2–5% neutrophils, <1% eosinophils and basophils (5). At least 3 weeks after the acute episodes, an allergological study was performed. Skin prick tests were performed with irbesartan (150 mg/ml), HCT (50 mg/ml), and latex in patient 1, and amiloride (5 mg/ml), HCT (50 mg/ml) and latex in patient 2. All drugs were tested in three healthy control subjects. All skin tests elicited negative results. Single-blind oral challenge tests with irbesartan in patient 1 and amiloride in patient 2 were negative. A basophil activation test using CD63 as a marker for activated basophils (Basotest®, ORPEGEN Pharma, Heidelberg, Germany) was performed with HCT, including dilutions from 50 µg/ml to 50 mg/ml. An activation of 21.9%, of CD63 activated basophils, for patient 1 and an activation of 20.6% for patient 2 were obtained at 50 mg/ml

concentration (baseline activation of 9.2% and 4.6%, respectively). A maximum basophil activation of 10.4% at a 50 mg/ml concentration was obtained in a control subject. Gamboa et al. (6) describe a negative Basophil Activation Test at two concentrations of hydrochlorothiazide (0.025 and 1 mg/ml) in a patient with acute noncardiogenic pulmonary edema caused by hydrochlorothiazide. The discrepancy with our results may be due to the concentration used, as we obtained positive results at higher concentration.

In conclusion, we describe two cases of noncardiogenic HCT-induced pulmonary edema in which positive results in basophil activation test were obtained, suggesting basophil participation in the reaction and its potential role as a diagnostic tool. The results of a bronchoalveolar lavage in one of the patients seem to corroborate the hypothesis that neutrophenia may occur because of pulmonary sequestration of neutrophils, although the mechanisms involved remain unknown.

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References

1. Goetschalckx K, Ceuppens J, Van Mieghem W. Hydrochlorothiazide-associated noncardiogenic pulmonary oedema and shock: a case report and review of the literature. *Acta Cardiol* 2007;**62**:215–220.

2. Torné Cachot J, Peñarrubia María MT, Moner Coromina L. Non-cardiogenic acute pulmonary edema and recurrent leukopenia caused by hydrochlorothiazide. *Rev Clin Esp* 2001;**201**:107–108.
3. Watrigant Y, Wallaert B, Ramon P, Gosselin B, Peng W, Tonnel AB. Subacute pneumopathy caused by hydrochlorothiazide. Cytologic study of the broncho-alveolar lavage. *Rev Mal Respir* 1986;**3**:227–229.
4. Vereda A, Cárđaba B, Quirce S, de las Heras M, Cuesta J, Sastre J. Immunological studies in a case of hydrochlorothiazide induced pulmonary edema. *J Invest Allergol Clin Immunol* 2006;**15**:297–298.
5. Balbi B, Pignatti P, Corradi M, Baiardi P, Bianchi L, Brunetti G et al. Bronchoalveolar lavage, sputum and exhaled clinically relevant inflammatory markers: values in healthy adults. *Eur Respir J* 2007;**30**:769–781.
6. Gamboa PM, Achotegui V, Irigoyen J, Pérez-Asenjo J, Merino J, Sanz ML. Hydrochlorothiazide-induced acute non-cardiogenic pulmonary edema. *J Investig Allergol Clin Immunol* 2005;**15**:299–301.